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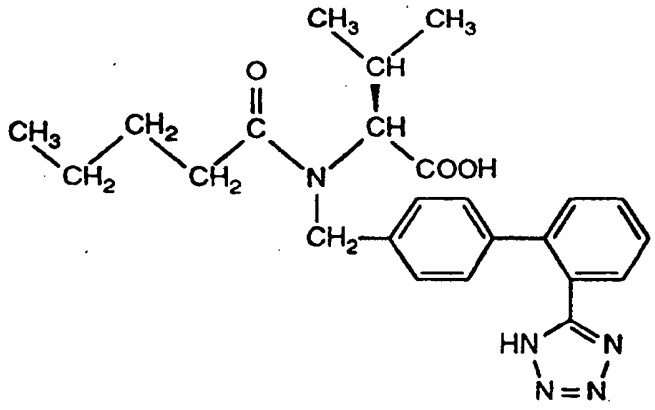
Published
With international search report.

(54) Title: TREATMENT OF DIABETIC NEPHROPATHY WITH VALSARTAN

(57) Abstract

The angiotensin II antagonist of formula (I) and the pharmaceutically acceptable salts thereof can be used for the therapeutic treatment of diabetic nephropathy.



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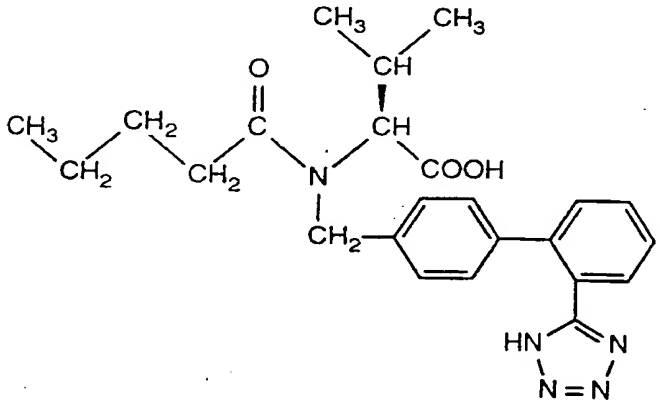
Treatment of diabetic nephropathy with Valsartan

In patients who, for example, have been suffering from Diabetes mellitus for a relatively long time, vascular disorders of the kidneys are frequently observed. One of the symptoms observed is diabetic nephropathy, also called diabetic glomerulosclerosis. Nodular thickenings in the glomerular loops cause constrictions of the vascular lumen, fibrinoid deposits in the capillary walls and microaneurisms. Such pathological symptoms manifest themselves clinically in the form of massive proteinuria and hypertension. If the diabetic nephropathy is not suitably treated, renal function will deteriorate to the terminal stage, which requires dialysis.

Great importance is therefore attached to the search for active ingredients that are able either to act preventively to halt the course of the diabetic nephropathy in suitable manner, or to reduce the symptoms.

PCT Application WO 92/10182 (publication date: 25.06.92) describes the use of angiotensin II antagonists for the treatment of diabetic nephropathy. In that Application, especially N-containing heterocycles, more especially imidazole derivatives, and also peptide angiotensin II antagonists are described as being advantageous for the treatment of diabetic nephropathy.

Extensive pharmacological studies have shown that the angiotensin II antagonist of formula



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and the pharmaceutically acceptable salts thereof are suitable, to a surprising degree, for the therapeutic treatment of diabetic nephropathy. The compound of formula (I) and the pharmaceutically acceptable salts thereof can also be used in prophylaxis. Those prop-

erties are obtained especially by means of systemic administration of the active ingredient.

The compound (I) can be especially in the form of pharmaceutically acceptable salts. Since the compound (I) has, for example, at least one basic centre, it can form acid addition salts. Those salts are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanecarboxylic acids, for example acetic acid, unsaturated or saturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, for example aspartic or glutamic acid, or benzoic acid, or with organic sulfonic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkane- or -arylsulfonic acids, for example methane- or p-toluene-sulfonic acid. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonium or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropyl-amine, or a mono-, di- or tri-hydroxy-lower alkylamine, for example mono-, di- or tri-ethanolamine. Corresponding internal salts can also be formed.

In the European Patent Application published under No. 443 983 (publication date: 28.08.91), in Example 16, the compound of formula (I) and the salts thereof, which compound differs not only structurally from the compounds shown in WO 92/10182, is described specifically [(S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]amine] and characterised as an angiotensin II antagonist. The angiotensin II antagonising properties of that compound are likewise disclosed in that Application.

Further, the compound of formula (I) or the salts thereof are distinguished by excellent tolerability and unexpectedly pronounced strength of activity.

The ability to treat diabetic nephropathy with the aid of the compound of formula (I) or the pharmaceutically acceptable salts thereof can be demonstrated, for example, in the following animal model which is known to the person skilled in the relevant field of the art.

Thus, for example, the short term and long term effects, induced by the blocking of angiotensin II, on the development of glomerular lesions can be determined after administration of the test compound to hyperglycaemic diabetic rats. The method used is analogous to the test method described in *J. Am. Nephrol. 1993, 4: 40-49.* A therapeutic effect is present, for example, when, in such diabetic rats, the increase in the glomerular filtration rate (GFR) is prevented and proteinuria and glomerulosclerosis are avoided.

The effect of long-term treatment with an angiotensin II blocker can be determined in normotensive rats in which diabetes has been induced by injection of streptozotocin (e.g. 45 mg/kg i.v.).

The glomerular filtration rate and the renal plasma flow can be measured as clearance of ^{3}H-inulin or ^{131}I-hippurate. The antitrophic effect of the angiotensin II blocker of formula (I) on vascular hypertrophy, which is a secondary symptom of diabetes, can be determined by measuring both the mesenteric vascular weight and the glomerular volume analogously to *Diabetes 1990, 39, p. 1575-1579.*

Similarly advantageous effects can be obtained in the treatment of glomerulosclerosis associated with hyperlipidaemia.

In prophylaxis, the compound of formula (I) that can be used according to the invention and the pharmaceutically acceptable salts thereof can help to prevent the pathological symptoms that occur in diabetic nephropathy, for example the formation of lesions of the vascular system in the kidney and the increase in pressure in the glomerular capillaries, and therefore offers protection against glomerular, haemodynamic and structural abnormalities in the kidney and thus ensures stabilisation of the renal functions. Further, with the aid of the compound of formula (I) that can be used according to the invention and of the pharmaceutically acceptable salts thereof, the occurrence of the pathological symptoms occurring in diabetic nephropathy, for example proteinuria, glomerulosclerosis, glomerular hypertrophy and high glomerular capillary pressure, can be slowed down, lessened or reversed. Thus, abnormal glomerular and haemodynamic effects can be corrected and normalised.

The present invention relates to the use of the compound of formula (I) and of the pharmaceutically acceptable salts thereof for the preparation of pharmaceutical compositions for

the treatment of diabetic nephropathy.

The present Application relates also to a method for the treatment of diabetic nephropathy, which comprises administering to patients requiring such treatment a therapeutically effective amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof.

The present Application relates also to pharmaceutical compositions for the treatment of diabetic nephropathy, which compositions comprise a therapeutically effective amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient suitable especially for systemic administration.

The invention therefore relates also to corresponding systemically administrable pharmaceutical compositions which comprise as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A therapeutically effective amount is understood to be the amount which halts or reduces the progress of the disorder diabetic nephropathy or completely cures the disorder, or which acts preventively. Such an amount can be determined without difficulty by the person skilled in the relevant art.

Those pharmaceutical compositions are for enteral, such as oral or rectal, or parenteral administration to warm-blooded animals, the compositions comprising the pharmacological active ingredient on its own or together with conventional pharmaceutical excipients. The pharmaceutical compositions comprise, for example, from approximately 0.1 % to 100 %, preferably from approximately 1 % to approximately 60 %, active ingredient. Pharmaceutical compositions for enteral and parenteral and also for ocular administration are, for example, those in unit dose form, such as dragées, tablets, capsules or suppositories, and also ampoules. They are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose,

mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, gum tragacanth, methyl-cellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical compositions are dry-filled capsules made of gelatin and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, with stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may likewise be added.

There come into consideration as rectally administrable pharmaceutical compositions, for example, suppositories that consist of a combination of active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that comprise a combination of the active ingredient and a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable for parenteral administration are especially aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used

suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, also stabilisers.

The dose of the active ingredient can depend on various factors, such as the mode of administration, the species of warm-blooded animal, age and/or individual condition. In normal cases, the approximate daily dose for a patient weighing about 75 kg is estimated to be, in the case of oral administration, from approximately 10 mg to approximately 250 mg.

The present Application relates also to a process for the preparation of pharmaceutical compositions for the treatment of diabetic nephropathy, which compositions comprise the compound of formula (I) or a pharmaceutically acceptable salt thereof.

The following Example illustrates the invention described above but is not intended to limit the scope thereof in any way.

Formulation Example 1: A hard gelatin capsule comprising as active ingredient, for example, (S)-N-(1-carboxy-2-methylprop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine can be formulated, for example, as follows:

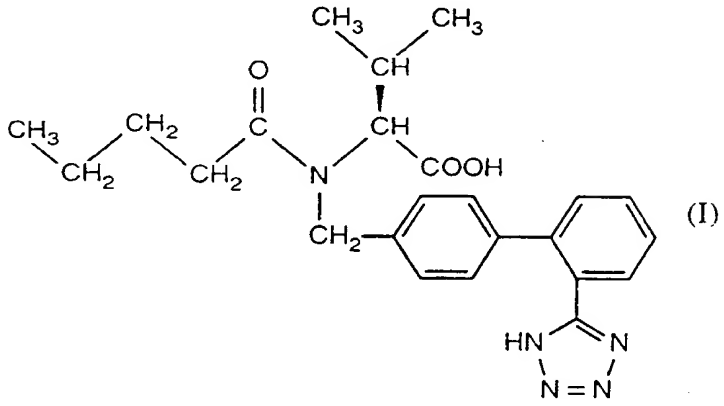
Composition

(1) active ingredient	80.0 mg
(2) microcrystalline cellulose	110.0 mg
(3) polyvidone K30	45.2 mg
(4) sodium lauryl sulfate	1.2 mg
(5) crospovidone	26.0 mg
(6) magnesium stearate	2.6 mg

Components (1) and (2) are granulated with a solution of components (3) and (4) in water. Components (5) and (6) are added to the dry granules and size 1 hard gelatin capsules are filled with the resulting formulation.

What is claimed is:

1. The use of a compound of formula (I)



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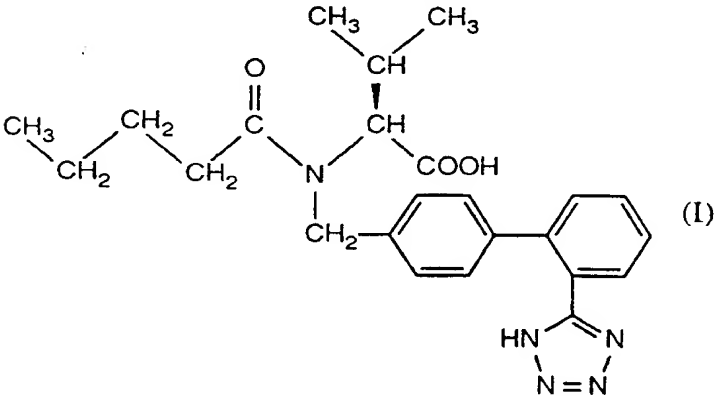
or a pharmaceutically acceptable salt thereof for the preparation of pharmaceutical compositions for the treatment of diabetic nephropathy.

2. A method of treating diabetic nephropathy, which comprises administering to patients requiring such treatment a therapeutically effective amount of a compound of formula (I)



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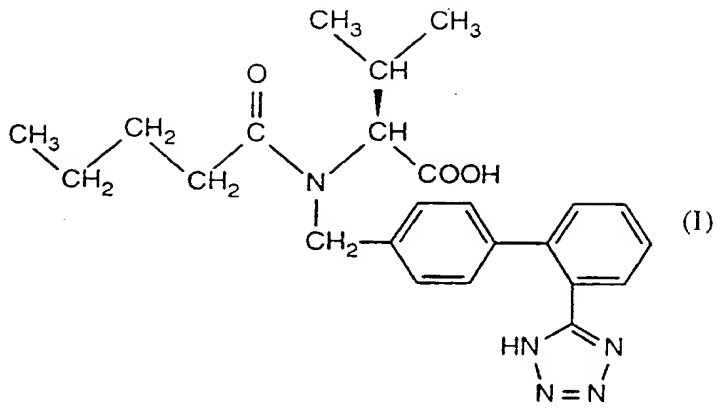
or of a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition for the treatment of diabetic nephropathy, comprising a therapeutically effective amount of a compound of formula (I)



(I)

or of a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

4. The use of a compound of formula (I) or of a pharmaceutically acceptable salt thereof according to claim 1 for the preparation of a pharmaceutical composition for the therapeutic and prophylactic treatment of glomerular, haemodynamic and structural abnormalities in the kidney, of proteinuria, of glomerulosclerosis, of glomerular hypertrophy and of high glomerular capillary pressure.

5. A method according to claim 2 for the therapeutic and prophylactic treatment of glomerular, haemodynamic and structural abnormalities in the kidney, of proteinuria, of glomerulosclerosis, of glomerular hypertrophy and of high glomerular capillary pressure.

6. A pharmaceutical composition according to claim 3 for the treatment of glomerular, haemodynamic and structural abnormalities in the kidney, of proteinuria, of glomerulosclerosis, of glomerular hypertrophy and of high glomerular capillary pressure.

INTERNATIONAL SEARCH REPORT

Intern. ial [redacted]tcation No
PCT/EP 95/00831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO,A,93 15732 (CIBA-GEIGY AG) 19 August 1993 see the whole document ---	3,6 1,2,4,5
X Y	EP,A,0 443 983 (CIBA-GEIGY AG) 28 August 1991 cited in the application see page 5 see example 16 see claims 34-36 ---	3,6 1,2,4,5
X Y	HYPERTENSION (UNITED STATES), JUN 1993, VOL. 21, NO. 6 PT 2, PAGE(S) 1056-61, Wood JM et al 'Kidney is an important target for the antihypertensive action of an angiotensin II receptor antagonist in spontaneously hypertensive rats.' see the whole document --- -/--	3,6 1,2,4,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 May 1995	26. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Stierman, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR J PHARMACOL (ENGLAND), OCT 1993, VOL. 110, NO. 2, PAGE(S) 761-71, Criscione L et al 'Pharmacological profile of valsartan: a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype.' see the whole document	3,6
Y	---	1,2,4,5
Y	WO,A,91 14367 (E.I. DU PONT DE NEMOURS AND COMP.) 3 October 1991 see page 25	1,2,4,5
Y	--- J AM SOC NEPHROL (UNITED STATES), JUL 1993, VOL. 4, NO. 1, PAGE(S) 40-9, Remuzzi A et al 'Short- and long-term effect of angiotensin II receptor blockade in rats with experimental diabetes.' see the whole document	1,2,4,5
Y	--- 75TH ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ATLANTA, GEORGIA, USA, APRIL 21-25, 1991.;& FASEB (FED AM SOC EXP BIOL) J,, VOL. 5, NO. 5, PAGE(S) A1039, 1991. WOLF G et al 'GLUCOSE-INDUCED CELLULAR HYPERTROPHY IN CULTURED PROXIMAL TUBULE CELLS ENHANCEMENT BY ANGIOTENSIN II AII' see abstract	1,2,4,5
Y	--- WO,A,92 10182 (SMITH-KLINE BEECHAM PLC) 25 June 1992 cited in the application see the whole document	1,2,4,5
A	--- DE,A,30 26 402 (SYNTEX CORP.) 4 February 1982 see the whole document	1,2,4,5

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 95/00831

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see attached sheet!

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP95/00831

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

1. subject-matter excluded from Patentability:
Although claims 2 and 5 are directed to a method of treatment of the human /animal body (Art 52(4)EPC) the search has been carried out and based on the alleged effect of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. al [redacted]cation No
PCT/EP 95/00831

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9315732	19-08-93	AU-B-	3722493	03-09-93
		CA-A-	2128324	19-08-93
		EP-A-	0626846	07-12-94
		NO-A-	942756	22-07-94
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		EP-A-	0524946	03-02-93
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		JP-T-	6503343	14-04-94
DE-A-3026402	04-02-82	NONE		